(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00185 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/EP00/05541

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914745.6 24 June 1999 (24.06.1999) GB

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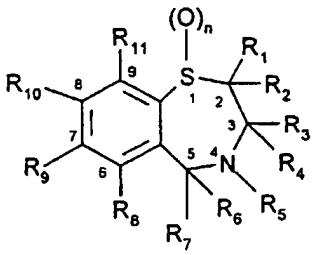
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC AGENTS



(I)

(57) Abstract: The present invention provides a method of treating obesity and related conditions comprising the administration to a mammal, particularly a human, in need thereof of a therapeutically effective amount of a compound of formula (I) in which: n=0, 1 or 2; R_1 and R_2 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo); R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, a phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo; R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula $-S(O)_pR_{14}$ in which p=1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo; R_6 and R_7 are each H; R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo; their stereoisomers; and pharmaceutically acceptable salts thereof.

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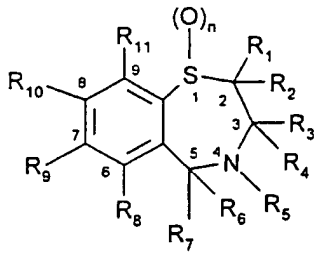
Therapeutic Agents

The present invention relates to the use of 2,3,4,5-tetrahydro-1,4-benzothiazepines in the treatment of obesity, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation.

Compounds of formula I



I

in which:

n = 0, 1 or 2;

R_1, and R_2 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl andalkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula -$S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_6 and R_7 are each H;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon

atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;

their stereoisomers; and

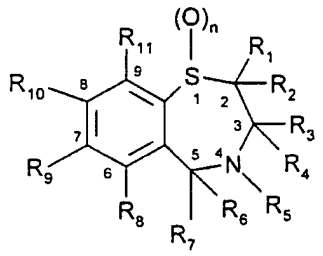
pharmaceutically acceptable salts thereof;

with the proviso that:

(i) when n = 0; at least one of R_1 to R_{11} is other than H;

are disclosed in WO94/11360 for the treatment of seizures and neurological disorders.

The present invention provides a method of treating obesity and related conditions comprising the administration to a mammal, particularly a human, in need thereof of a therapeutically effective amount of a compound of formula I



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R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula -$S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_6 and R_7 are each H;

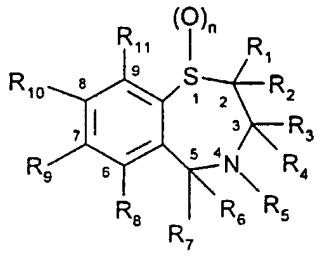
R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof.

The term "related conditions" as used herein means eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation.

In a preferred group of compounds of formula I



I

n is 0 or 1;

R_1, R_2, R_6 and R_7 are each H;

R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, or when R_3 and R_4 are independently H or methyl, R_5 is H, methyl, formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

R_8 is H, methyl, fluoro or chloro; and

R_9, R_{10} and R_{11} are each H;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of formula I are selected from:
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine; and
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and pharmaceutically acceptable salts thereof.

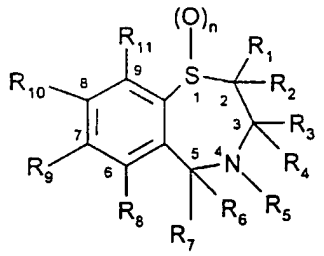
More preferred compounds of formula I are selected from:
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine; and
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and pharmaceutically acceptable salts thereof.

Most preferred compounds of formula I are selected from:
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide; and

6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and pharmaceutically acceptable salts thereof.

A particularly preferred compound of formula I is:
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
its stereoisomers; and pharmaceutically acceptable salts thereof.

The present invention also provides pharmaceutical compositions for the treatment of obesity and related conditions comprising a therapeutically effective amount of compounds of formula I



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in which:

n = 0, 1 or 2;

R_1, and R_2 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl andalkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula -$S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_6 and R_7 are each H;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon

atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;
their stereoisomers; and
pharmaceutically acceptable salts thereof;
with the proviso that:
(i) when n = 0; at least one of R_1 to R_{11} is other than H;
together with a pharmaceutically acceptable diluent or carrier.

Preferred pharmaceutical compositions for the treatment of obesity and related conditions comprise a therapeutically effective amount of compounds of formula I in which:
n = 0 or 1;
R_1 and R_2 are independently H or methyl;
R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;
R_5 is H or methyl, and when R_3 and R_4 are H or methyl, R_5 is H, methyl, formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;
R_6 and R_7 are each H; and
one of R_8 to R_{11} is H, fluoro, chloro, bromo, iodo, methyl (optionally substituted with one or more halo), methoxy (optionally substituted by one or more halo), nitro, cyano, carboxy, acetyl, dimethylcarbamoyl or dimethylsulphamoyl; the remainder of R_8 to R_{11} being H;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

More preferred pharmaceutical compositions for the treatment of obesity and related conditions comprise a therapeutically effective amount of compounds of formula I in which:
n = 0 or 1;
R_1, R_2, R_6 and R_7 are each H;
R_3 and R_4 are H, or together are methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, and when R_3 and R_4 are H, R_5 is H, methyl, formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl, or ethylsulphonyl;

R_8 is H, methyl, fluoro or chloro;

R_9 to R_{11} are all H;

their stereoisomers; and

pharmaceutically acceptable salts thereof.

Especially preferred pharmaceutical compositions for the treatment of obesity and related conditions comprise a therapeutically effective amount of compounds of formula I selected from:

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiapine 1-oxide;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-benzoyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;

6-chloro-4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

The compounds of the present invention may prepared and formulated into pharmaceutical formulations as described in WO94/11360.

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 1000 mg preferably 1 to 500 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to

give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Preferably the tablets and capsules each contain 5, 10, 15, 20, 25, 30, 50,100 ,250 or 500mg.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all of the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I may be used to treat obesity and related conditions including eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress in mammals particularly humans, and as an aid to smoking cessation in human beings. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In yet another aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for use in the treatment of obesity and related conditions including eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation.

The present invention also provides a method of treating obesity and related conditions including eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia and stress which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

The present invention also provides a method of reducing the craving to smoke in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof. The present invention also provides a method of reducing weight gain after smoking cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

In addition the compounds of the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for example non exercise activity thermogenesis and increased metabolic rate.

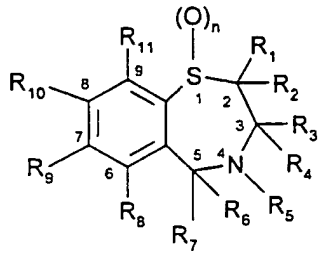
The compounds of the present invention may be useful in preventing cardio-vascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy and in aiding weight loss after smoking cessation.

The following *in vivo* test supports the finding that compounds of formula I have efficacy in the treatment of obesity.

Marmosets given 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (50 mg/kg po) daily for 14 days showed reduced bodyweight gain.

Claims

1) A method of treating obesity and related conditions comprising the administration to a mammal, particularly a human, in need thereof of a therapeutically effective amount of a compound of formula I



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n = 0, 1 or 2;

R_1, and R_2 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl andalkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula -$S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_6 and R_7 are each H;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the proviso that:

(i) when n = 0; at least one of R_1 to R_{11} is other than H;

together with a pharmaceutically acceptable diluent or carrier.

2) A method as claimed in claim 1 in which comprises a compound of formula I in which

n is 0 or 1;

R_1, R_2, R_6 and R_7 are each H;

R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, or when R_3 and R_4 are independently H or methyl, R_5 is H, methyl, formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

R_8 is H, methyl, fluoro or chloro; and

R_9, R_{10} and R_{11} are each H;

or a pharmaceutically acceptable salt thereof.

3) A method as claimed in claim 1 in which the compound of formula I is selected from:

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;

6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;

4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;

4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;

4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;

4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;

6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;

4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;

4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;

6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine; and

6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;

their stereoisomers; and pharmaceutically acceptable salts thereof.

4) A method as claimed in claim 1 in which the compound of formula I is selected from:

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine; and
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and pharmaceutically acceptable salts thereof.

5) A method as claimed in claim 1 in which the compound of formula I is selected from:

4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide; and
6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and pharmaceutically acceptable salts thereof.

6) A method as claimed in claim 1 in which the compound of formula I is selected from:

4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
and pharmaceutically acceptable salts thereof.

7) The use of a compound of Formula I as described in any one of claims 1-6 in the manufacture of a medicament for use in the treatment of obesity and related conditions including eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, and as an aid to smoking cessation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00185 A3

(51) International Patent Classification[7]: A61K 31/554, A61P 3/04, 3/06, 3/10, 25/34, 43/00

(21) International Application Number: PCT/EP00/05541

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914745.6 24 June 1999 (24.06.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
11 April 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,4-DENZOTHIAZEPINES TO TREAT OBESITY RELATED DISORDERS

(57) Abstract: The present invention provides a method of treating obesity and related conditions such as bulimia, anorexia, snacking, binge eating, non insolin dependent diabetes meltitus, hyperglycaemia, stress, hyperlipidaemia, and to aid to smoking cessation comprising the administration to a mammal, particularly a human, in need thereof of a therapeutically effective amount of a compound of formula (I) in which: n=0, 1 or 2; R_1 and R_2 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo); R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, a phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo; R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula-COR_{13} in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula -$S(O)_pR_{14}$ in which p=1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo; R_6 and R_7 are each H; R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo; their stereoisomers; and pharmaceutically acceptable salts thereof.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/554 A61P3/04 A61P3/06 A61P3/10 A61P25/34
A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, PAJ, EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 11360 A (THE BOOTS COMPANY) 26 May 1994 (1994-05-26) cited in the application the whole document	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2001	21/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; "Antihyperlipidaemic benzothiazepines" retrieved from DIALOG Database accession no. 1994184809 XP002183519 abstract & EXPERT OPINION ON THERAPEUTIC PATENTS_(_EXPERT OPIN. THER. PAT._), 1994, 4/6 (717-718), United Kingdom the whole document -----	7

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 (all partially)

   use of compounds of formula I in the manufacture of a medicament for the treatment of obesity and related conditions including bulimia, anorexia, snacking and binge eating

2. Claims: 1-7 (all partially)

   Use of compounds of formula I in the manufacture of a medicament for the treatment of non-insulin dependent diabetes mellitus or hyperglycemia

3. Claims: 1-7 (all partially)

   Use of compounds of formula I in the manufacture of a medicament for the treatment of hyperlipidemia

4. Claims: 1-7 (all partially)

   Use of compounds of formula I in the manufacture of a medicament for the treatment of stress

5. Claims: 1-7 (all partially)

   Use of compounds of formula I in the manufacture of a medicament as an aid for smoking cessation

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. In fact, the claim contains so many variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible.
Moreover the term "and related conditions" in claim 1 is neither sufficiently clear nor concise nor supported by the description.
Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely on the compounds of claims 2-6 and on obesity and conditions mentioned in claim 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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